1.0 SCIENTIFIC ABSTRACT OF THE PROTOCOL

Scientific Abstract

Cystic fibrosis (CF), the most common lethal genetic disease in North America, is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR gene product is required for regulation of epithelial chloride transport in multiple organs, including the airways. CF lung disease develops gradually over many years as abnormally viscous secretions lead to airways obstruction, infection, inflammation, and fibrosis. It ultimately may lead to respiratory failure, which is the cause of death in more than 90% of CF patients. A subset of patients with CF develop severe chronic sinusitis requiring bilateral antrostomies and monthly instillation of antibiotics in their sinuses for the suppression of symptomatic sinusitis. It is this patient subset which is the subject of our proposed study.

Gene therapy for CF lung disease is currently being pursued with adenovirus and liposome-based vectors. Although these vector systems are efficient for expression of CFTR both *in vitro* and *in vivo*, neither one results in stable DNA integration into the target cell. As a result, expression from each of these type of vectors is generally transient in nature. Since long-term expression is likely to be important for interrupting the progression of disease as outlined above, neither of the two current systems would seem to be optimal.

Targeted Genetics Corporation has developed an alternative vector system for CFTR gene transfer based on adeno-associated virus (AAV), tgAAVCF. AAV vectors can stably persist in the host cell, and AAV-CFTR vectors have been shown to confer long term correction of the physiologic defect in cAMP-mediated chloride secretion when administered to cultured CF bronchial epithelial cells. Furthermore, AAV-CFTR vectors transduce and express recombinant CFTR *in vivo* after delivery to the airway surface of animals. Long-term vector expression, up to 6 months after a single-dose administration, has been observed in the New Zealand white rabbit and rhesus monkey models.

An additional advantage of AAV vectors is the absence of any wild-type AAV viral coding sequence in the vector construct. Inflammatory reaction as a result of viral gene expression is not a possibility with AAV-CFTR vectors because of their lack of viral genes. Studies in rabbits, mice, rats, and rhesus macaques have all demonstrated that single-dose AAV vector administration does not result in lung inflammation or any other adverse effects, even at doses resulting in high levels of recombinant gene expression.

In this study, tgAAVCF is administered to CF patients with chronic sinusitis who have undergone bilateral antrostomies and are on a prophylactic antibiotic for prevention of symptomatic sinusitis. This study is divided in two parts. Part 1 is a dose-escalation safety study of tgAAVCF vector administration to the maxillary sinus epithelium. Doses will range from $1x10^2$ to $5x10^4$ replication units (RU) (equivalent to: $1x10^8$ to $5x10^{10}$ total particles). The purpose of Part 1 of this study is to determine the dose of tgAAVCF leading to at least 25% transfection of maxillary sinus epithelium. This dose will then be used in Part 2 to determine whether tgAAVCF administered to one maxillary sinus of a patient leads to clinical and physiologic improvement when compared to placebo administered to the contralateral sinus of the same patient in the absence of antibiotic prophylaxis. The results of this study will serve to guide dosing and endpoints to be used in future clinical trials.